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Short title: Expert consensus on managing multiple sclerosis in the Gulf

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Abstract

Recent research has expanded our understanding of the natural history and clinical course of multiple sclerosis (MS) in the Arabian Gulf region. In addition, the number of available therapies for MS has increased greatly in recent years, which complicates considerably the design of therapeutic regimens. We, an expert group of physicians practising in Arabian Gulf countries, present pragmatic consensus recommendations for the use of disease modifying therapy, according to the level of MS disease activity, according to objective criteria, and prior treatment (if any) received by a given patient.

Key words: multiple sclerosis; disease-modifying therapy; consensus statement

Introduction

Our knowledge of the epidemiology and clinical characteristics of multiple sclerosis (MS) in the Arabian Gulf region has expanded considerably in recent years. The region has been traditionally regarded as a low-risk area for MS, but epidemiological studies over the last two decades have demonstrated an MS prevalence of 55–85/100,000 population across individual Gulf states.[1] Moreover, the prevalence of MS appears to have increased in the Gulf recently, and is generally present with a medium or high prevalence there.[1-3] Multiple barriers to the achievement of optimal MS care in the Middle East have been identified previously and have been reviewed elsewhere.[4] In the current article, we set out to provide an expert consensus on the use of DMD-based therapy at different stages of the trajectory of MS.

MS is a lifelong, neurodegenerative disease with the potential for long-term disability, which requires accurate diagnosis, early treatment and monitoring and intensive lifelong management. Accordingly, MS presents a considerable, and probably increasing, public health challenge to the healthcare systems of the Gulf states. It is important that appropriate local guidance is available for physicians to manage MS, but until recently the region had been largely overlooked by guideline writers. This was rectified to some extent by the publication of comprehensive guidance from the Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS), updated in 2019.[5]

Guidance specifically for Gulf countries is lacking, however, and the treatment landscape has changed in recent years. For example, new treatments have become available, and access to these treatments has improved.[5-8] We know more about the potential safety profiles of disease-modifying drugs (DMDs), leading to a better understanding of the risks of highly active DMDs for MS, including mitigating the risk of progressive multifocal leukoencephalopathy (PML) with natalizumab and other MS treatments, and a reassessment of the role of alemtuzumab in MS therapy.[9,10] Also, we have increased knowledge of the efficacy of DMDs in MS patients with varying underlying disease activity, which will contribute to better personalised MS care.[11]

Periodic updating of guidance for the management of MS is helpful for regions where this disease presents a public heath priority. Accordingly, we, a group of physicians based in the Gulf with special expertise on MS management, present our consensus recommendations on the management of MS in the region, with a special focus on the use of DMDs according to patients' MS treatment history and current MS disease activity. Our main focus is on relapsing-remitting MS (RRMS), as a number of effective treatments are now available for the management of this form of MS. We also address briefly current pharmacologic management options for clinically isolated syndrome (CIS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).

Methods

The expert consensus described in this article arose from a closed meeting (in Muscat, Oman, April 2019) in which all authors participated; delegates from Kuwait, Oman, Bahrain, Qatar

and the United Arab Emirates participated. The consensus is supported here by a narrative review, based on presentations at this meeting, supplemented by additional literature searches and material provided by co-authors. The level of consensus on recommendations within the expert group was explored by open voting: "high" level of consensus was defined arbitrarily as supported by at least 7 out of 10 experts, moderate consensus was defined as being supported by 4–6 out of 10 experts, and lower support was defined as a "low" level of consensus, i.e. 3 or experts or fewer. The objective of this consensus is to establish recommendations that would support the treating physicians in the Gulf region in the management of MS patients according to the level of disease activity taking into account several other factors such as efficacy, safety, monitoring burden, life style and pregnancy.

Brief overview of currently available disease-modifying therapies for relapsing-remitting MS

Prescribing DMDs in the Gulf region

Guideline-driven prescribing practices differ somewhat in the Gulf region, compared with other regions. In practice, prescribing guidance in the Gulf follows that in the country where the pharmaceutical sponsor of the drug is located (e.g. for fingolimod, EMA is used as the template for guidance, as its sponsor is located in Basel, Switzerland). Guidelines proposed by expert societies in Europe or in the USA, for example, reflect the prescribing guidance relevant to those countries, e.g. with respect to which DMD can be prescribed for a patient new to therapy, and which should be reserved for patients already exposed to one or more DMDs. The situation is more fluid in the Gulf. In principle, any DMD could be prescribed for any patient, subject to certain restrictions, such as local formulary policies or budgetary restraints. This situation supports the generation of management recommendations local to the Gulf, such as those proposed in our article.

In addition, the current guideline for the wider region of the Middle East and North Africa (MENACTRIMS) supports the use of off-label therapies under some conditions, e.g. to use a DMD without a specific indication for MS in place of a licensed drug of a similar mechanism,[5] For clarity, we have restricted our discussions to DMDs with a specific indication for use in MS.

Overview of DMDs

The efficacy, tolerability and safety of DMDs have been reviewed extensively elsewhere.[5,12] For the purposes of this article, discussion of the properties of individual DMDs will be brief, and Table 1 provides a brief overview of their administration, efficacy and safety.[13-32] DMDs approved for the management of relapsing-remitting MS (RRMS) are often classified into broad groups. "First-line" or "platform" agents usually refer to interferons, glatiramer acetate and teriflunomide, while "high-efficacy" agents usually include fingolimod, alemtuzumab, natalizumab, ocrelizumab and cladribine tablets.[5,12] Dimethyl fumarate may be intermediate between these categories, as there is some evidence that the efficacy of this agent is similar to that of fingolimod.[33,34]

In general, as outlined in Table 1, the use of high-efficacy DMDs compared with platform agents may be expected to involve an individualised trade off between more effective suppression of relapses (with some evidence of greater potential for amelioration of long-term progression of disability, based on evaluation of progression of EDSS scores). Randomised, head-to-head comparisons of DMDs are uncommon, but such comparisons of alemtuzumab,[13,24] ocrelizumab,[25,32] or fingolimod[27] with interferons support greater efficacy for the highly efficacious DMDs. With regard to safety (Table 1), an increased risk of autoimmune diseases has been associated with rebound of immune cells after their suppression by alemtuzumab. New contraindications relating to concomitant autoimmune and cardiovascular diseases have also been applied to alemtuzumab in Europe (see below).[35] Natalizumab (in particular) has been associated with increased risk of PML (especially in a JC virus-positive patient, and/or after prolonged treatment). Ocrelizumab is associated with infusion reactions that require administration to take place in a clinic setting with facilities to deal with severe or even life-threatening events. Fingolimod may induce severe cardiovascular abnormalities (bradycardia, with or without cardiac conduction block). Fingolimod and cladribine tablets carry a warning of potential for malignancy in their US or European labelling, although recent analyses suggest little or no additional risk of malignancy with cladribine tablets.[36-38] Several agents are associated with an increased risk of infections associated with their suppression of the immune system.

Further, DMDs may be classified according to the World Health Organization into immune modulators (interferons), immune stimulators (glatiramer acetate) and selective immunosuppressants (teriflunomide, fingolimod, natalizumab, ocrelizumab, alemtuzumab, and cladribine tablets).[39] Immunosuppressant DMDs that are given chronically exert long-term suppression of the immune system.

Immune reconstitution therapies has emerged as a further classification of DMDs.[40] These agents (cladribine tablets and alemtuzumab are hypothesised to act in this manner) are given as two short courses one year apart (Table 1), and their efficacy in suppressing MS disease activity in responders to treatment far outlasts both this period of administration.[40] Further treatment courses of alemtuzumab beyond the initial two courses may be given if required, but there is no requirement for further treatment with cladribine tablets beyond this two year period, according to its labelling (see Table 1). Ocrelizumab is an antibody directed against the CD20 antigen: this mechanism is also consistent with immune reconstitution, based on observations with rituximab, which shares this mechanism.[41,42] However, the pivotal trials that evaluated ocrelizumab involved continuing, 6-monthly administration of this DMD,[25,32] so that the potential for ocrelizumab as an immune reconstitution therapy has yet to be demonstrated clinically.[41,42]

Consensus recommendations for the management of RRMS

Classifying disease activity in RRMS

Previous classifications of disease activity

The European labelling for DMDs approved for the management of MS supports the prescription of high-efficacy DMDs in patients with active or highly active disease (Table 2), but the definitions of "active" or "highly active" disease differ between individual DMDs. Alemtuzumab and natalizumab are recommended for use in the USA only after unsuccessful treatment with at least one DMDs, which in practice will restrict their use to patients with high disease activity. In addition, a recent review of the safety of alemtuzumab has led to a restriction of its use in Europe to patients with highly active or rapidly worsening MS.[32]

Recommendations on classification of RRMS disease activity at first presentation

No universally accepted definition of disease activity in MS exists. Accordingly, we present our own consensus recommendation on pragmatic criteria for that can be readily applied to the individual patient in the routine clinical situation, and which are useful for guiding therapy. In doing so, we considered the merits of previous approaches to this problem. As an example of the European approach to classifying MS disease activity, four classifications of "high disease activity" were considered by the EMA in reaching their consensus on the labelling of cladribine tablets. These considerations were based on relapse rates and radiologic findings, including consideration of whether patients had received prior treatment with a DMD or not.[43] A management algorithm proposed by the National Health Service (NHS) in England, UK, proposes three levels of RRMS disease activity for consideration when proposing the use of an individual DMD.[44] The first category contains patients with two significant relapses within the previous two years, with others containing patients with one relapse in the last two years with currently evolving radiologic activity, and finally rapidly evolving severe MS, defined as "two or more disabling relapses in one year and one or more gadolinium-enhancing (Gd+) lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI".

A merit of the NHS and EMA approaches, in the opinion of the authors, is their avoidance of subjective terms such as "mild" or "moderate". Such terms are often used in classifications of MS severity,[45] but may have different leaning for different readers and in the experience of the authors it will often be difficult to classify patients into one category or the other in routine clinical practice. Accordingly, we propose the use of three categories of disease activity to guide therapy for a patient with RRMS, modified from the criteria described above:

Patients with active MS. These patients will have had one relapse in the last 1 year, or two relapses in the last 2 years, but do not have poor prognostic indicators. This category replaces the "low" or "mild" disease group usually used in disease activity classifications.

Patients with highly active disease. This group contains patients with at least two relapses in the previous year and more than nine T2 lesions, or ≥1 Gd+ lesion without an impact on EDSS (i.e. no residual disabilities after steroid treatment)

Patients with rapidly evolving severe RRMS. These patients have had at least one disabling relapse, with impact on EDSS score (i.e. residual disabilities), or with MRI lesions

in strategic prognostic areas (spinal cord, cerebellum, brain stem), or poor prognostic factors (see below). A disabling relapse, as defined by NHS England,[44] is described in Box 1.

The categories cannot be entirely prescriptive, given the heterogeneity of presentation of MS, and it is important to note that the experience and judgement of the expert physician remains important here. Presentation at onset is important: for example, optic neuritis is usually considered a less severe presentation, while spinal/brainstem/cerebellar presentations are considered more severe and may help to place a patient into a higher disease activity category. Consideration of prognostic indicators indicating likely progression of disease can also help to identify a patient with highly active disease. It is important to integrate demographics, clinical and prognostic information into the management of the patient.

In future, biomarkers may help to identify patients with higher disease activity in need of more intensive treatment. Recent data suggest that blood neurofilament light chain may be a promising candidate for such a biomarker, among others, and further research will be needed to validate their therapeutic use in the delivery of personalised MS care.[11,46]

Treatment recommendations

Table 3 summarises our recommendations regarding the use of DMDs at different MS disease activities, and according to prior receipt of DMD-based MS care. All patients with active RRMS need treatment with a DMD, and only these patients are considered here. In general we follow the convention of reserving high-efficacy DMDs for patients with higher levels of disease activity, or for patients who have already experienced disease recurrence on one or two DMDs previously.

Where poor prognostic indicators are not present, the platform DMDs (interferon-beta, glatiramer acetate, teriflunomide, dimethyl fumarate [DMF]) are recommended as first-line therapy in a DMD-naïve patient with MS. For second line treatment, where a switch of DMD was necessitated by breakthrough MS disease activity, agents of higher efficacy are recommended (cladribine tablets, DMF, fingolimod, or natalizumab). Ocrelizumab, fingolimod and alemtuzumab, have demonstrated greater activity vs. a platform DMD in randomised trials, as described above.[13-25,27-29,32] DMF may be considered for these patients as there is some evidence for greater efficacy compared with other platform therapies.[20,47] Another post-hoc analysis of data from the CLARITY trial suggested that cladribine tablets had greater efficacy vs. placebo across a range of baseline demographic and disease subgroups, including MS disease duration and absence of prior DMD treatment.[48] We also considered that a switch of DMD due to a tolerability or patient preference issue may be achieved via a new DMD of similar efficacy, but a different mechanism (a "lateral switch").

No choice of third-line treatment is evidence based, due to the lack of well designed clinical trials based on patients who have received two DMDs previously, and so these recommendations are from the experience and judgement of the authors. It is reasonable that a patient with breakthrough activity on two previous DMDs will need the most effective therapy available. For this reason, DMF is omitted from this category, and ocrelizumab and

alemtuzumab are added. A recent network meta-analysis found comparable efficacy for suppression of relapses and progression of disability between other highly-effective DMDs,[49] which adds support to this approach. The prescribing of alemtuzumab has been restricted in Europe to patients with highly active disease, with new contraindications relating to concomitant autoimmune and cardiovascular conditions (see Tables 1 and 2).

Most DMDs are contraindicated during pregnancy and breastfeeding. This is a large subject in its own right, and a detailed account of options for the patient who is, or is planning, pregnancy is outside the scope of our review. An expert group from the UK has recently provided a detailed set of recommendations on the care of MS patients with regard to family planning, and we recommend this to readers who require more information on this subject.[50]

Identifying and managing suboptimal response in RRMS

There is no evidence base from randomised clinical trials for defining sub-optimal response and subsequent decision of switching/ escalation from second-line therapies. Published guidance (e.g. from NHS England, see above[44]) defines suboptimal treatment response on the basis of no reduction in relapse frequency after a suitable time on treatment. However, the identification of a suboptimal treatment response does not necessarily mean that DMD treatment should inevitably change. The definitions of suboptimal response based on our expert opinion and presented in Table 4 may prompt action short of stopping/switching DMD treatment, e.g. scheduling further follow-up MRI. Increased EDSS without new MRI lesions may imply a condition of transitional progressive MS other than RRMS. This needs to be verified before changes in treatment and likely need at least 3-6 months to confirm the progression and define the disease course (i.e. secondary progressive).

The labelling for high efficacy DMDs specifies situations in which they may be prescribed, including with regard to previous DMD treatment, washout periods vary greatly between DMDs. The mechanism of action of a DMD may dictate the washout time as some of the DMDs such as fingolimod since the peripheral lymphocyte count may be helpful in predicting the return of sequestered lymphocyte. However, undue delay may increase the risk of disease reactivation and the management of potential disease reactivation after stopping fingolimod or natalizumab is important.[51] Patients should be counselled carefully to contact their healthcare team immediately on the occurrence of new symptoms after stopping these treatments.[52]

The mechanisms of action, pharmacokinetics and pharmacodynamics of a DMD may provide important information relating to the need or otherwise to switch a treatment. The application of immune reconstitution therapy is a case in point, where two year treatment courses are required for cladribine tablets or alemtuzumab (possibly longer for alemtuzumab). We recommend finishing the 2-year course even if a relapse occurs during the first year of treatment before judging the efficacy of such immune reconstitution DMDs..

Composite scores such as modified RIO scores may be useful tools for evaluation of response to treatment in MS.[53] These scores were derived from cohorts of patients treated with beta-

interferon, however, and further research is needed to confirm the extent to which we can use these tools to predict response to different treatments.

Pharmacologic management of other forms of MS

Clinically isolated syndrome

Criteria for the diagnosis of CIS have been updated recently,[54] and a substantial proportion of patients previously considered to have had CIS would be diagnosed with MS under these current criteria.[55] Randomised trials have demonstrated that treatment with one of several DMDs delayed to a statistically significant extent the conversion of CIS (as diagnosed using contemporaneous criteria) to clinically definite MS (reviewed elsewhere[56]). Interferon-beta is indicated for use in CIS in the USA, and in Europe for people with "a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis" (see table 2 for a summary of therapeutic indications for DMDs). The authors endorse this evidence-based use of interferon-beta in CIS. Teriflunomide significantly reduced the rate of conversion to clinically definite MS by about half relative to placebo in a population with CIS, in a randomised trial supported by an extension phase.[57,58] Glatiramer acetate also reduced the rate of conversion from CIS to clinically definite MS during three years of follow-up in a randomised trial in 481 patients, published in 2009.[59]

Most DMDs are approved for the management of CIS in the USA (Table 2). This indication in the USA appears to be based on a general effect on relapsing forms of MS without evidence gathered from a population of patients who had CIS *per se*

Secondary progressive MS

The US labelling for DMDs now supports their use for "relapsing forms of multiple sclerosis", which provides a broader indication that for RRMS *per se* and include relapsing forms of secondary MS, although not all of these indications are strongly evidence-based (Table 2). The use of siponimod in active SPMS is supported by evidence from a randomised trial, as described above. Interestingly, a 96-week, randomised Phase 2 study (ONWARD) randomised patients with active RRMS or SPMS despite treatment with interferon-beta to additional cladribine tablets or placebo.[60] A subgroup analysis suggested efficacy in patients with RRMS or active SPMS within this population. There was consensus in our group to support the use of siponimod and cladribine tablets in active SPMS. Our expert group did not endorse the use of interferon-beta for active SPMS as the data on this agent are conflicting given the negative results of a European long-term study.[61]

Primary progressive MS

Therapeutic options in PPMS are severely limited. Ocrelizumab has an indication for PPMS in the USA. Its EU label supports use in early PPMS where imaging shows inflammatory activity. The EU label is consistent with the results of a subgroup of the ORATORIO Phase

3 trial, which demonstrated a trend towards greater efficacy in patients with Gd+ lesions at baseline, vs. patients without Gd+ lesions, although the trial was not powered to provide a definitive comparison of outcomes between these subgroups.[62]

Discussion

The expansion of treatment options for RRMS in recent years has included a number of newer agents with greater efficacy in suppressing MS disease activity, compared with platform therapies, such as interferons and glatiramer acetate. Baseline prognostic indicators play a major role in the treatment decision and they help in stratifying the patients to different DMDs. In principle, high efficacy DMDs were tested either against comparators such as IFNs (Fingolimod Vs. IFNB 1a IM, Ocrelizumab & Alemtuzumab Vs. IFNB 1a SC) or accumulated real world data have provided scientific evidence of being superior to platform therapies in case of Natalizumab. With respect to Cladribine tablets, only the post-hoc subgroup analysis has supported its use in highly active patients; however, the real world data is still lacking given its recent approval. Furthermore, regulatory authorities in the US and Europe approved Cladribine tablets for highly active MS patients.

There is currently no universally accepted consensus on the definition of high disease activity in MS, however, with recommendations on the use of individual DMDs largely driven by the design of their pivotal clinical trials Thus, taking into account the level of evidence based on clinical trials/ systematic review, labelling of the DMDs by regulatory authorities, real world evidence supported by post-marketing data along with the expert opinions, we have proposed a set of criteria for defining disease activity in a given patient, based on available definitions and clinical experience. Although, the primary focus of this manuscript was on how to select DMDs based on prognostic indicators and disease activity, other factors such as long-term safety, monitoring burden, life style/ compliance, and pregnancy are important to consider when initiating/escalating DMDs. This exercise was necessary for the development of our consensus recommendations on which DMDs are most suitable for use at each level of disease activity, and according to the patient's prior treatment history. The consensus is intended to assist the treating physicians in the Gulf region in the stratification of the expanding available armamentarium of DMDs.

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Box 1. NHS England definition of a disabling MS relapse.[44]

- Affects the patient's social life or occupation, or is otherwise considered disabling by the patient
- Affects the patient's activities of daily living as assessed by an appropriate method
- Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others
- Needs treatment/hospital admission.

Table 1. Overview of key properties of currently available DMDs for use in patients with MS.

	Efficacy	Overview of typical side-effects[a]	Administration
Beta interferons See note b	Risk reductions for relapses vs. placebo of 27%–33% (21 to 44) Reduced accumulation of long-term disability vs. placebo in some studies (based on EDSS progression)	Psychological disturbances, hepatic disturbances, influenza-like symptoms. Caution where there is history of seizures or CV disease.	**Injection**: IFNβ1a: 30 µg i.m. QW IFNβ1b: 44 µg TIW by s.c. injection (22 mg TIW if higher dose is not tolerated)
Glatiramer acetate (GA)[17,18]	29–34% reduction in risk of relapses for GA vs. placebo Improved EDSS category in one study	Flushing and CV disturbances occur on administration (usually resolves). Convulsions, anaphylaxis and serious hypersensitive reactions are rare.	**Injection**: 20 mg s.c. QD
Dimethyl fumarate (DMF)[19,20]	Relative risk reductions vs. placebo of 44–53% vs. placebo (different dosing regimens) and 29% vs. GA Significant reduction in likelihood of 1-step EDSS progression Greater likelihood of NEDA on DMF vs. placebo	Typically flushing, gastrointestinal side-effects. Severe, prolonged lymphopenia may occur. PML has been reported associated with prolonged lymphopenia.	**Oral**: 120 mg BID titrated to recommended maintenance dose of 240 mg BID
Teriflunomide[21,22]	Lower relapse (by 31–36%), disability accumulation and MRI progression vs. placebo	Abnormal LFTs, alopecia, gastrointestinal disturbances, elevated BP, skin reactions (possibly severe).	**Oral**: 14 mg QD
Alemtuzumab[23,24]	50–78% reduction in relapses vs. interferon-beta$_{1a}$; more relapse free at 2 y vs. interferon in one study in patients with breakthrough disease despite treatment ($p<0.0001$) Similar sustained disability accumulation, but more NEDA vs. interferon	Infusion-associated reactions in >90%. Autoimmune conditions are common (now contraindicated in autoimmune conditions other than MS). Risk of serious cardiovascular side-effects.[c] Risk of Infections (mainly herpes simplex, varicella zoster and listeriosis)	**Infusion**: 1st course: 12 mg/day on 5 consecutive days 2nd treatment course: 12 mg/day on 3 consecutive days 12 months after the first treatment course. Up to two more courses can be given

Cladribine tablets[25,26]	58% reduction in relapse rates and 2.53-fold chance of being disease free vs. placebo at up to 4 y More with no change in 3-month EDSS and more with NEDA vs. placebo	Mainly lymphopenia/leukopenia, and opportunistic infections (mainly varicella zoster). Screen carefully for latent TB. Label has warning on malignancy (see text). PML has been noted on other cladribine regimens.[d]	**Oral**: 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days or QD treatment, depending on body weight.
Fingolimod[27,28]	Reduced annualised relapse rates ($p<0.001$)[e] and more relapse free, vs. placebo or i.m. interferon Greater likelihood of no disability progression or NEDA vs. placebo only	Bradycardia and transient intracardiac conduction delays are the principal side-effect. Also potential for opportunistic infections, macular oedema, raised liver function tests. Possible increased risk of malignancy, especially of the skin	**Oral**: 0.5 mg QD (0.25 mg QD for children ≤40 kg body weight)
Natalizumab[29,30]	Reduction in relapses (by 68%) over 1 y and reduction in sustained disability progression over 2 y vs. placebo	Risk of PML, especially in JCV+ patients and after long-term administration; also risk of other, potentially serious opportunistic infections. Also hepatic disturbance. Risk of Immune Reconstitution Inflammatory Syndrome on withdrawal.	**Infusion**: 300 mg infused every 4 weeks
Ocrelizumab[31,32]	46% reduction in annualised relapses over 1 y (vs. s.c. interferon-beta$_{1a}$)	Infusion reactions may be severe or even life-threatening. PML has been observed with another drug of similar mechanism (rituximab)	**Infusion**: Initial 600 mg dose followed by 300 mg 2 weeks later, then 600 mg 6-monthly. Premedicate to reduce severity of infusion reactions.[f]

Statements on efficacy are from randomised, Phase 3 clinical trials cited, statements on side-effects are abstracted and pooled from US and European labelling. [a]Brief overview only – consult your local labelling for a full account of side-effects, contraindications and warnings/precautions over use. [b]Includes interferon-beta$_{1a}$, interferon-beta$_{1b}$. [c]New European CV contraindications include uncontrolled hypertension, angina pectoris, myocardial infarction, stroke or dissection of the cervicocephalic arteries, coagulopathy, use of antiplatelet or anti-coagulant therapy. [d]Refers to higher dose, parenterally-administered regimens used in the management of leukaemias. [e]Annual relapse rates 0.16–0.18 vs. 0.40 on placebo, and 0.16–0.20 vs. 0.33 on i.m. interferon-beta$_{1a}$. [f]Give 100 mg i.v. methylprednisolone (or an equivalent) 30 min before infusion and antihistamine 30–60 minutes prior to infusion; consider antipyretic 30–60 min prior to infusion (EU label). BP: blood pressure; BID: twice daily; CV: cardiovascular; JCV+: John Cunningham virus positive; PML: Progressive multifocal leukoencephalopathy; QD: once daily; QW: once weekly; TB: tuberculosis; TIW: three times weekly.

Table 2. Therapeutic indications for DMDs used in the management of MS

DMD	US Food and Drug Administration	European medicines Agency
Interferon-beta$_{1a}$ and interferon-beta$_{1b}$	Relapsing forms of MS[a]	CIS[c] and active relapsing MS (≥2 attacks in previous 2 years)
Glatiramer acetate	Relapsing forms of MS[a] in adults	Relapsing forms of MS (excludes secondary forms of MS)
Dimethyl fumarate	Relapsing forms of MS[a]	RRMS
Teriflunomide	Relapsing forms of MS[a]	RRMS
Alemtuzumab	Relapsing forms of MS[b] in adults (generally for patients with inadequate response to ≥2 other DMDs)	Highly active RRMS[d] (despite ≥1 prior DMD) or if disease is worsening rapidly[d]
Cladribine tablets	Relapsing forms of MS[b] in adults (generally for patients uncontrolled by/ intolerant to another DMD)	Adults with highly active RRMS defined by clinical or imaging features
Fingolimod	Relapsing forms of MS[a] (≥10 y)	Highly active RRMS[c] (≥10 y)[d]
Natalizumab	Relapsing forms of MS[a] (generally after inadequate response to ≥2 other DMDs)	Highly active RRMS[d]
Ocrelizumab	Relapsing forms of MS[a] Primary progressive forms of MS	Relapsing forms of MS with active disease Early PPMS with MRI evidence of inflammation

[a]Specifically includes clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS) and active secondary progressi e MS (SPMS). [b]RRMS and active SPMS. [c]Defined in EU label as "single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis". [d]Defined as highly active disease despite a full and adequate course of treatment with at least one DMD *or* rapidly evolving severe RRMS (≥2 disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions or a significant increase in T2 lesion load as compared to a previous recent MRI). [e]Restriction applied by European regulator in November 2019 (see text).Abstracted from US and European labelling. Indications are paraphrased for brevity, see labels for full wording.

Table 3. Consensus recommendations on the use of DMDs in people with RRMS according to disease activity and previous treatment status.

Disease activity at first presentation	Treatment recommendation		
	No prior DMD (1st-line)	**1 prior DMD (2nd-line)**	**2 prior DMD (3nd-line)**
Active MS without indicators of poor Prognosis	Beta Interferon Glatiramer acetate Teriflunomide Dimethyl fumarate	Cladribine tablets Dimethyl fumarate Fingolimod Natalizumab[b]	Cladribine tablets Natalizumab Fingolimod Ocrelizumab Alemtuzumab[b]
Highly active MS	Cladribine tablets Natalizumab Fingolimod Ocrelizumab Dimethyl fumarate[a]	Cladribine tablets Natalizumab Ocrelizumab Alemtuzumab[a,c] Fingolimod[a]	Cladribine tablets Natalizumab Ocrelizumab Alemtuzumab[c]
Rapidly evolving severe MS	Cladribine tablets Natalizumab Ocrelizumab Fingolimod[a]	Natalizumab Ocrelizumab Alemtuzumab[a,c] Cladribine tablets[a]	Natalizumab Fingolimod Ocrelizumab

All recommendations were achieved via a high level of expert consensus (at least seven out of ten experts agreed), except where indicated as [a]moderate consensus (between four and six experts agreed) or [b]low consensus (three experts or fewer agreed). DMD: disease-modifying drug. [c]New restrictions on the prescribing of alemtuzumab were applied in Europe in November 2019 (see text).

Table 4. Actions recommended for specific manifestations of suboptimal treatment response

Suboptimal response after 1 year of 1st line treatment:	**Action recommended**
A single MRI lesion in a strategic location (spinal cord, cerebellum, brain stem) or ≥3 MRI lesions in non-strategic locations. Single relapse (non-disabling), without EDSS progression[a] or MRI activity.	This may prompt scheduling further follow-up MRI at 6 months or Lateral switching to other DMD (with different mechanism of action) but this depends on the overall presentation (consider a higher efficacy DMD)
MRI progression + relapse EDSS progression + relapse	Switching DMD treatment

[a]Usually defined as progression by 1 point for EDSS <5, or 0.5 points if EDSS ≥5.

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